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10/727,580	12/05/2003	Guy Sauvageau	765/12810.186	7319

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EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
04/06/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/727,580	SAUVAGEAU ET AL.	
	Examiner	Art Unit	
	JENNIFER DUNSTON	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 January 2009 and 19 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7,9,12,13,18,20,23,26 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7,9,12,13,18,20,23,26 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 June 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/13/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/13/2009 has been entered.

Receipt is acknowledged of an amendment, filed 1/13/2009, in which claim 12 was amended. Claims 7, 9, 12, 13, 18, 20, 23, 26 and 27 are pending.

Any objection or rejection of record in the previous office actions not addressed herein is withdrawn.

Election/Restrictions

Applicant elected Group II with traverse in the reply filed on 6/29/2006. Applicant elected the species HOXB4 with traverse in the reply filed on 10/2/2006.

Currently, claims 7, 9, 12, 13, 18, 20, 23, 26 and 27 are under consideration.

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 1/13/2009, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action.

Claim Objections

Claims 9, 20, 26 and 27 are objected to because of the following informalities: the claims refer to "the amino acid sequence" rather than "the stem cell expansion factor." It is clear that the amino acid sequence refers to the stem cell expansion factor; however, consistent claim terminology should be used. Appropriate correction is required. This is a new objection.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 7, 9, 12, 13, 18, 20, 23 and 26-27 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 36 and 38 of copending Application No. 10/530,413 (hereinafter the '413 application). This rejection was made in the Office action mailed 7/28/2008 and has been rewritten to address the amendments to the claims in the reply filed 1/13/2009.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 7, 9 and 26 are generic to all that is recited in claim 36 of the '413 application. That is, claim 36 of the '413 application fall entirely with the scope of claims 7, 9 and 26 of the instant application or, in other words, instant claims 7, 9 and 26 are anticipated by claim 36 of the '413 application. Claim 36 of the '413 application is narrower in scope than the instant claims in that it requires the use of the product of claim 15 which comprises additional elements relative to the product use by the method of the instant claims. Specifically, the conflicting claim requires the HOXB4 peptide comprising a HIV PTD from a transactivation protein (TAT), and a blocker, which reduces the expression level of at least one gene normally limiting HOX-induced expansion of stem cells. Furthermore, conflicting claim 38 requires the cells to be human or mouse hematopoietic stem cells. Thus, an obvious variant of conflicting claim 36 is where the cells are human hematopoietic cells. Accordingly, instant claims 12, 13, 18, 20, 23 and 27 are not patentably distinct from the conflicting claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Arguments - Double Patenting

With respect to the rejection of claims 7, 9, 12, 13, 18, 20, 23 and 26-27 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 36 and 38 of copending Application No. 10/530,413, Applicant's arguments filed 1/13/2009 have been fully considered but they are not persuasive.

The response notes that Applicant does not wish to address the double patenting rejection at this time, because the instant application is the earlier filed application and may be permitted to issue as a patent if the provisional double patenting rejection is the only rejection present. Because the case is not in condition for allowance at this time, the rejection is maintained.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 9, 12, 13, 18, 20, 23, 26 and 27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This is a new rejection.

Claim 7 is vague and indefinite in that the metes and bounds of the phrase "a NH_2-terminal protein transduction domain (PTD) from a transactivating protein (TAT)" are unclear. It is unclear if the PTD is from any transactivating protein (e.g., transcription factor) or whether the PTD is from HIV TAT. Transcription factors such as VP16 contain a transactivation domain (e.g., specification, page 40, lines 30-31). The HIV TAT protein is a transcription factor that transactivates the viral genome (e.g., specification, paragraph bridging pages 7-8). Further, the specification teaches that other transcription factors contain PTDs (e.g., page 7). Accordingly, the metes and bounds of the claim are unclear.

Claims 9, 12, 13 and 26 depend from claim 7 and thus are indefinite for the same reasons as applied to claim 7.

Claim 18 is vague and indefinite in that the metes and bounds of the phrase "a NH_2-terminal protein transduction domain (PTD) from a transactivating protein (TAT)" are unclear. It is unclear if the PTD is from any transactivating protein (e.g., transcription factor) or whether the PTD is from HIV TAT. Transcription factors such as VP16 contain a transactivation domain (e.g., specification, page 40, lines 30-31). The HIV TAT protein is a transcription factor that transactivates the viral genome (e.g., specification, paragraph bridging pages 7-8). Further, the specification teaches that other transcription factors contain PTDs (e.g., page 7). Accordingly, the metes and bounds of the claim are unclear.

Claims 20, 23 and 27 depend from claim 18 and thus are indefinite for the same reasons as applied to claim 18.

Response to Arguments - 35 USC § 112

The rejection of claims 12 and 13 under 35 U.S.C. 112, second paragraph has been withdrawn in view of Applicant's amendment to the claims to depend from a pending claim in the reply filed 1/13/2009.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 7, 9, 12, 13, 18, 20, 23, 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Largman et al (US Patent No. 5,837,507, cited on the IDS filed 8/17/2005) in view of Frankel et al (US Patent No. 5,804,604, cited in a prior action; see the entire reference). This rejection was made in the Office action mailed 7/28/2008 over claims 7, 9, 18, 20, 23, 26 and 27 and has been extended to claims 12 and 13.

Largman et al teach the expression of an exogenous HOX gene, preferably HOXB4, in a stem cell to generate expanded population of pluripotent stem cells *in vitro* or *in vivo* (e.g., Abstract; column 2, lines 35-59; column 8, lines 5-38; column 11, line 53 to column 12, line 50). The preferred stem cell is a hematopoietic stem cell, such as a human hematopoietic stem cell expressing the cell surface marker CD34 (e.g., column 2, lines 48-59). Largman et al teach that it is the expression of the HOXB4 gene (i.e., the HOXB4 protein) that results in the desired function (e.g., column 12, lines 5-37).

Largman et al do not teach the method where the HOXB4 protein is delivered to the stem cell by crossing the cell membrane as a result of the presence of a HIV-TAT protein.

Frankel et al teach the delivery of biologically active proteins to the cytoplasm and nuclei of cells *in vitro* and *in vivo* by the use of transport polypeptides which comprise HIV TAT protein, which are covalently attached to the cargo protein (e.g., Abstract; column 1, lines 20-40; column 2, line 64 to column 4, line 3; column 7, lines 23-38). Frankel specifically teach the delivery of a transcription factor by TAT mediated protein transduction (e.g., column 12, lines 25-40). Further, Frankel et al teach that methods of DNA delivery typically deliver the nucleic acid molecules into only a fraction of the total cell population and tend to damage large numbers of cells (e.g., column 1, lines 54-63). In contrast, the methods of using the TAT protein to

deliver proteins provide efficient delivery of non-TAT proteins that are not inherently capable of entering target cells or nuclei, or are not inherently capable of entering cells at a useful rate (e.g., column 3, lines 6-15).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of generating expanded populations of stem cells of Largman et al to replace the delivery of HOXB4 protein by delivering a nucleic acid molecule with the delivery of HOXB4 protein by delivering a TAT-conjugated protein as taught by Frankel et al because Largman et al teach it is within the ordinary skill in the art to use HOXB4 protein expression to expand populations of stem cells and Frankel et al teach the delivery of proteins to cells *in vitro* and *in vivo*.

One would have been motivated to make such a modification in order to receive the expected benefit of more efficiently delivering the HOXB4 protein to the cells as taught by Frankel et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 7, 9, 12, 13, 18, 20, 23, 26 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Largman et al (US Patent No. 5,837,507, cited on the IDS filed 8/17/2005) in view of Nagahara et al (Nature Medicine, Vol. 4, No. 12, pages 1449-1452, December 1998, cited as reference #3 on the IDS filed 8/17/2005; see the entire reference). This is a new rejection.

Largman et al teach the expression of an exogenous HOX gene, preferably HOXB4, in a stem cell to generate expanded population of pluripotent stem cells *in vitro* or *in vivo* (e.g., Abstract; column 2, lines 35-59; column 8, lines 5-38; column 11, line 53 to column 12, line 50). The preferred stem cell is a hematopoietic stem cell, such as a human hematopoietic stem cell expressing the cell surface marker CD34 (e.g., column 2, lines 48-59). Largman et al teach that it is the expression of the HOXB4 gene (i.e., the HOXB4 protein) that results in the desired function (e.g., column 12, lines 5-37).

Largman et al do not teach the method where the HOXB4 protein is delivered to the stem cell by crossing the cell membrane as a result of the presence of a HIV-TAT protein transduction domain.

Nagahara et al teach that the introduction of cDNA expression vectors results in a low percentage of cells targeted (e.g., page 1449, left column, 1st paragraph). To address this problem, Nagahara et al describe the development of a full-length protein transduction method using urea-denatured, genetic in-frame TAT fusion proteins, which can be applied to a broad spectrum of proteins regardless of size or function (e.g., page 1449, left column 3rd paragraph). Nagahara et al teach a bacterial expression vector, pTAT-HA, to produce genetic in-frame TAT fusion proteins (e.g., page 1449, left column, 4th paragraph; Figure 1). The pTAT-HA vector comprises an N-terminal 6-histidine leader followed by the 11-amino-acid TAT protein transduction domain flanked by glycine residues, a hemaglutinin (HA) tag and a polylinker (e.g., page 1449, left column, 4th paragraph; Figure 1). Nagahara et al teach the cloning, expression and isolation of the TAT-fusion proteins (e.g., page 1449, paragraph bridging columns; page 1452, box; Figure 1). Nagahara et al teach that TAT fusion proteins are readily transduced into

all cells present in whole blood and bone marrow stem cells (e.g., paragraph bridging pages 1449-1450). Nagahara et al teach that misfielded TAT fusion proteins efficiently transduce into ~100% of cells in a rapid, concentration-dependent manner, are refolded *in vivo* and retain known biological and biochemical activities (e.g., page 1450, right column, last full paragraph). Further, Nagahara et al teach that the disclosed method allows for the purification and use of recombinant proteins that are insoluble and present in inclusion bodies of bacteria (e.g., page 1452, left column). Moreover, the urea-denaturation allows appears to enhance the delivery of the proteins into cells (e.g., page 1452, left column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of generating expanded populations of stem cells of Largman et al to replace the delivery of HOXB4 protein by delivering a nucleic acid molecule with the delivery of HOXB4 protein by delivering a TAT-conjugated protein as taught by Nagahara et al because Largman et al teach it is within the ordinary skill in the art to use HOXB4 protein expression to expand populations of stem cells and Nagahara et al teach that delivery of TAT-fusion proteins can overcome the problem of inefficient delivery by cDNA expression vectors.

One would have been motivated to make such a modification in order to receive the expected benefit of more efficiently delivering the HOXB4 protein to the cells as taught by Nagahara et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

With respect to the rejection of claims 7, 9, 12, 13, 18, 20, 23, 26 and 27 under 35 U.S.C. 103(a) as being unpatentable over Largman et al in view of Frankel et al, Applicant's arguments filed 1/13/2009 have been fully considered but they are not persuasive.

The response asserts that it was not routine experimentation to produce a functional stem cell expansion factor which comprised a HOXB4 protein and a NH_2-terminal protein transduction domain (PTD) from a transactivating protein (TAT). The response points to Applicant's previous response and the Declaration of Dr. Humphries.

With respect to unpredictability, the declaration of Dr. Humphries notes that the inventors believe they were the first to use the TAT motif to transfer protein into hematopoietic stem cells (HSCs). However, it was known in the art that fusion proteins comprising TAT PTD were capable of introducing proteins into every cell of the blood and hematopoietic stem cells from bone marrow (Nagahara et al. Nature Medicine, Vol. 4, No. 12, pages 1449-1452, December 1998, cited as reference #3 on the IDS filed 8/17/2005; e.g., paragraph bridging pages 1449-1450). Further, the declaration of Dr. Humphries states that four to six months were necessary to generate the first TAT-HOXB4 protein due to the time needed to overcome hurdles including methods of production, purification and storage, dosage (amount and frequency), *in vitro* conditions, and nature and characterization of starting cells that would respond. "[A]n extended period of experimentation may not be undue if the skilled artisan is given sufficient direction or guidance." *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977). In the instant case, the prior art contains sufficient guidance for one to make the TAT-HOXB4 protein required for the method. The present specification states, "Using the pTAT-HA plasmid developed by

Nagahara et al. (1998), we will subclone a full-length Hoxb4 cDNA in frame and downstream to the His6-TAT-HA tag. The protein will be produced in bacteria and purified exactly as described by Nagahara (1998)." See page 35, lines 7-11. Nagahara et al teach the application of the prior art HIV TAT protein transduction domain (e.g., work done by Frankel et al) to a broad spectrum of proteins regardless of size or function (e.g., page 1449, left column, paragraph 3). Further, Nagahara et al teach that their protocol achieves two goals: first, it allows for the use of insoluble proteins present in inclusion bodies of recombinant bacteria; and second, urea-denaturation improves transduction of the proteins (e.g., page 1452, left column, 1st full paragraph). Thus, the level of knowledge and skill at the time of the invention was high such that one would know how to overcome obstacles related to insoluble protein for the making and purification of the TAT-HOXB4 protein. To apply known techniques to the HOXB4 protein would have been routine in the art at the time the invention was made and would not have required undue experimentation. The time necessary for routine experimentation or optimization does not establish that the invention was unpredictable.

The response asserts that many factors influence the success of tat-fusion protein delivery and tat-fusion protein function, including 1) cell type; 2) the fusion protein itself (which may affect protein folding, function, cellular localization, etc.; 3) the purification method of the TAT-fusion protein; and 4) the toxicity of the TAT-fusion protein . Thus, the response asserts that no reasonable expectation of success can be predicted by looking at the structure of the particular tat-fusion protein.

With respect to the cell type and subcellular localization, the response asserts that the subcellular localization may depend on cell type, nature of the imported proteins and delivery

approach for a given TAT-fusion protein. The response cites Yang et al as evidence of discrepancies observed between the localization of TAT-GFP and transfected GFP.

These arguments are not found persuasive. Yang et al note the controversial results in the art regarding the localization of TAT-GFP in cells that taken up TAT-GFP by transduction across the plasma membrane of the cell (e.g., page 42, section 3.4). GFP does not contain a nuclear localization signal sequence (NLS), and any nuclear localization would be dependent upon the NLS present in the TAT PTD peptide (e.g., page 36, paragraph bridging columns). Thus, Yang et al demonstrate that a translocated protein may localize to its native cellular compartment rather than the nucleus. However, HOX proteins were known in the art to be present within the nucleus without the addition of a heterologous NLS (Corsetti et al. Journal of Cell Science, Vol. 108, pages 187-193, 1995). Accordingly, one would expect some HOXB4 protein to be present in the nucleus due to the processes that localize endogenous HOXB4 to the nucleus and/or due to the presence of a NLS in the TAT PTD. Furthermore, the post-filing art teaches that HOXB4 is capable of translocating across the plasma membrane without an HIV TAT PTD (pages 1423-1424, Secreted HOXB4 binds DNA in human hematopoietic cells (Amsellem et al. Nature Medicine, Vol. 9, No. 11, pages 1423-1427, November 2003). The translocated HOXB4 protein has mixed nucleocytoplasmic localization, which is sufficient to amplify human hematopoietic progenitors (e.g., page 1424). Moreover, it was known in the art that fusion proteins comprising TAT PTD were capable of introducing proteins into every cell of the blood and hematopoietic stem cells from bone marrow (Nagahara et al. Nature Medicine, Vol. 4, No. 12, pages 1449-1452, December 1998, cited as reference #3 on the IDS filed 8/17/2005; e.g., paragraph bridging pages 1449-1450). Thus, there would have been an

expectation of success with regard to delivering TAT-HOXB4 to the nucleus of a hematopoietic progenitor cell.

With respect to toxicity, delivery and function, the response asserts that whether the TAT fusion protein would be functional and/or toxic would be unpredictable. The response cites Reis et al as evidence that a TAT-FMRP protein was taken up slowly and was toxic to fibroblasts.

This argument is not found persuasive. Schwarze et al (Science, Vol. 285, pages 1569-1572, September 1999, cited as reference #4 on the IDS filed 8/17/2008) teaches the injection of a mouse with 1 mg of a TAT PTD fusion protein per kilogram of body weight each day for 14 consecutive days produced no signs of gross neurological problems or systemic distress (page 1572, paragraph bridging left and middle columns). Thus, the TAT protein does not appear to be toxic. However, the art teaches that cells are particularly sensitive to the levels of FRMP protein in that reduced levels, as well as increased levels, of the protein result in an abnormal phenotype in mice (Peier et al. Human Molecular Genetics, Vol. 9, No. 8, pages 1145-1159, 2000). In contrast, the art specifically teaches increasing the level of HOXB4 protein in a cell to enhance the proliferation of stem cells (Largman et al. US Patent No. 5,834,507). As noted by Applicant, El-Andaloussi et al show that cellular uptake and cytotoxicity of cell-penetrating peptides depend upon the particular cargo delivered by the cell-penetrating peptide. Furthermore, the response cites Spitere et al as showing not toxicity following TAT-PAX6 protein transduction. Like HOXB4, PAX6 contains a homeodomain and is involved in stimulating cellular proliferation (Warren et al. Cerebral Cortex, Vol. 9, No. 6, pages 627-635, September 1999). Moreover, the response cites Falnes et al as showing that a diphtheria toxin A fragment could not be transported by TAT. The teachings of these references are consistent with toxicity of TAT-FMRP being due

to the FMRP portion of the fusion protein, while TAT-PAX6 is not toxic. Given HOXB4 contains its own homeodomain, which can act as a cell penetrating peptide, and the prior art teaches the advantages of increased protein in stem cells, there is no expectation for TAT-HOXB4 to be toxic or incapable of being transported across the membrane by TAT.

The response asserts that the mere availability of a method does not make it routine, and when several alternatives are possible, undue experimentation may be required to finally find a successful alternative. This argument is not found persuasive, because one would expect any protein transduction domain, not only HIV TAT, to be capable of transporting HOXB4 across the plasma membrane to stimulate stem cell proliferation. Thus, there would not be undue experimentation to identify the successful alternative.

The response asserts that there was a long-felt need for a method that would be able to significantly increase the number of patients who truly have access to successful HSC transplantation, and in particular those who do not find an HLA matched donor. The response points to paragraph 8 of the Declaration submitted April 17, 2008. The declaration of Dr. Roy indicates that patients in need for HSC transplantation include patients with blood cancer, solid tumors, and some non-malignant disorders, such as anemia, thalassemia or sickle cell anemia; however, 50% of patients in need for HSC transplantation do not find an HLA matched donor (paragraphs 3-5). The declaration notes that typically about 25% of patients in need of HSC transplantation find a donor amongst HLA matched siblings, and another 25% find a HLA matched unrelated donor (paragraph 5). The declaration characterizes the options available to those individuals lacking an HLA matched donor as the following: (1) transplantation of umbilical cord blood isolated stem cells, (2) transplantation of mismatched grafts, and (3)

autologous transfer of mobilized stem cells. Further, the response asserts that even if treatment is available, there remains a need to improve such treatments, because existing treatments are either not available or successful for many patients. Moreover, the response asserts that all of the mentioned available treatments would benefit from the present invention because it provides a way to increase the number of stem cells available for transplantation. The response asserts that Applicants have adequately established a long-felt need sufficient to overcome the rejection of record for the following reasons: 1) the need has been shown to be a persistent one that was recognized by those of ordinary skill in the art; 2) the long-felt need was not satisfied by another before the invention by applicant; and 3) the invention satisfies the long-felt need.

These arguments are not persuasive. The long-felt need is asserted to be a method to increase the number hematopoietic stem cells prior to transplantation. However, the claims are not limited to embodiments where hematopoietic stem cells are contacted with a TAT-HOXB4 protein *in vitro* prior to transplantation. Claims 7, 9, 12, 13, 18, 20 and 23 are drawn to or encompass embodiments where the protein is administered to stem cells *in vivo,* and claims 26-27 encompass the use of stem cells other than hematopoietic stem cells. Furthermore, the prior art teaches methods of hematopoietic stem cell expansion *in vitro*, where the methods comprise contacting a hematopoietic stem cell with a protein factor to stimulate the stem cells (e.g., US Patent No. 5,599,703, see the claimed invention; US Patent No. 5,668,104, see the claimed invention). Thus, the long-felt need was satisfied by another prior to applicant. Even if the long-felt need was not satisfied by another, the claims are not commensurate in scope with the long-felt need identified.

The response notes that the Examiner indicated that evidence of commercial success was not provided because the claimed invention is not commercially available. The response asserts that in the life science field, "commercial success" can be measured by the level of funding of a particular project by public and private instances, especially when the project is at the stage of entering clinical trials that are extremely costly. The response asserts that projects which provide new and improved treatment methods and fulfill an important need are supported. Thus, the response asserts that a strong measure of peer recognition is success in peer reviewed grant competitions for applications that include research into investigations of TAT-HoxB4 production/delivery and efficacy. Specific grants are cited by the response.

The Examiner maintains that because the invention is not commercially available, the evidence of record does not support the commercial success of the invention. Even if funding of research was equated with commercial success, the figures for funding do not show commercial success absent evidence as to the market share or whether the amounts are anything out of the ordinary in the field involved.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness. For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Response to Amendment – Declaration of Dr. Humphries

The declaration under 37 CFR 1.132 filed 4/17/2008 is insufficient to overcome the rejection of claims 7-13 and 18-23 based upon the Largman et al and Frankel et al references applied under 35 U.S.C. 103(a) as set forth in the last Office action.

It states that others failed when trying to achieve the claimed invention. However, there is no showing that others of ordinary skill in the art were working on the problem and if so, for how long. There is no showing that others of ordinary skill in the art were working to directly deliver HOXB4 protein to stem cells. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP § 716.04.

The declaration states that the subject matter of the invention is unpredictable and required more than routine experimentation to generate a TAT-HOXB4 protein for use in the claimed invention. This is not found persuasive for the reasons discussed above.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Response to Amendment – Declaration of Dr. Roy

The declaration under 37 CFR 1.132 filed 4/17/2008 is insufficient to overcome the rejection of claims 7-13 and 18-23 based upon the Largman et al and Frankel et al references applied under 35 U.S.C. 103(a) as set forth in the last Office action.

It states that the claimed subject matter solved a problem that was long standing in the art. However, there is no showing that others of ordinary skill in the art were working on the

problem and if so, for how long. There is no showing that others of ordinary skill in the art were working to directly deliver HOXB4 protein to stem cells. In addition, there is no evidence that if persons skilled in the art who were presumably working on the problem knew of the teachings of the above cited references, they would still be unable to solve the problem. See MPEP § 716.04.

The declaration does not provide evidence of commercial success, because the invention is not commercially available.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
Art Unit 1636

/JD/

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Primary Examiner, Art Unit 1636